Public Release Summary
on

Evaluation of the new active

TETRACONAZOLE

in the product

Domark 40ME Fungicide

Australian Pesticides and Veterinary Medicines Authority

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FOREWORD

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Ageing (Office of Chemical Safety), Department of Environment and Heritage (Risk Assessment and Policy Section) and State departments of agriculture and environment.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of public release summaries for all products containing new active ingredients and for all proposed extensions of use for existing products.

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the APVMA's publications *Ag Manual: The Requirements Manual for Agricultural Chemicals* and *Ag Requirements Series.*

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the APVMA and its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

More detailed technical assessment reports on all aspects of the evaluation of this chemical can be obtained by completing the order form in the back of this publication and submitting with payment to the APVMA. Alternatively, the reports can be viewed at the APVMA Library First Floor, 22 Brisbane Avenue, Barton, ACT.

The APVMA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Pesticides Program Manager, Australian Pesticides and Veterinary Medicines Authority, PO Box E240, Kingston ACT 2604.

CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
AHMAC	Australian Health Ministers Advisory Council
ai	active ingredient
BBA	Biologische Bundesanalstalt fur Land – und forstwirschaft
bw	bodyweight
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
Hct	Heamatocrit
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
id	intradermal
im	intramuscular
ip	intraperitoneal
IPM	Integrated Pest Management
iv	intravenous
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K_{oc}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be dquantified

mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
ng	nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
μg	microgram
vmd	volume median diameter
WG	Water Dispersible Granule
WHP	Withholding Period

INTRODUCTION

This publication provides a summary of data reviewed and an outline of the regulatory considerations for the proposed registration of DOMARK 40ME FUNGICIDE as a foliar spray to grapevines for the control of powdery mildew. The active constituent of the product is Tetraconazole which has been approved by the APVMA. It also seeks public comment prior to the chemical product being registered and approved for use in Australia.

Responses to public consultation will be considered prior to registration of the product detailed in this document. They will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

Copies of the full technical reports on public health, occupational health and safety, environmental impact and residues in food are available upon request.

Written comments should be received by the APVMA by 30 August 2005 and should be addressed to

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Active constituent

The chemical active constituent Tetraconazole has the following properties:

Common name (ISO):Tetraconazole

Chemical name: (*RS*)-2-(2,4-dichlorophenyl)-3-(1*H* –1,2,4-triazol-1-yl) propyl-1,1,2,2-tetrafluoroethyl ether

Tetraconazole has been approved by the APVMA as an active constituent (54972).

Formulated product

Product name: DOMARK 40ME

DOMARK 40ME FUNGICIDE is a group C fungicide suspension concentrate containing 40g/L technical tetraconazole. It is to be used as a foliar application to protect grapevines against powdery mildew.

CAS Registry Number: 112281-77-3

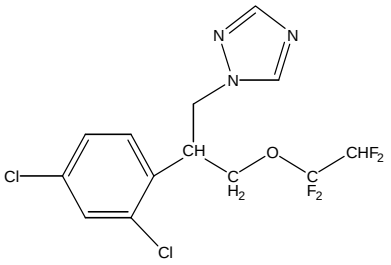
Empirical formula: $C_{13}H_{11}Cl_2F_4N_3O$

Molecular weight: 372.1

Density:1.055

Vapour pressure at 24^{o}C: 0.18mPa

Structural formula:



SUMMARY OF THE APVMA's EVALUATION OF DOMARK 40ME FUNGICIDE

The Chemistry and Residues Evaluation Section of the APVMA has evaluated the chemistry aspects of DOMARK 40ME FUNGICIDE (formulation, manufacturing process, quality control, batch analysis and analytical methods, and storage stability) and found them to be acceptable.

EVALUATION OF TOXICOLOGY

The toxicological database for tetraconazole, which consists primarily of toxicity tests conducted using animals, is quite extensive. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available. Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse health effects in humans would be expected.

Metabolism and Toxicokinetics

Following a single or repeated oral dose(s) (5 or 60 mg/kg bw) in rats, tetraconazole was extensively absorbed through the gastrointestinal tract (69-86%). The rate of absorption was lower in females and at higher dose levels, with peak concentrations occurring in the plasma from 1 to 28 hrs post-dosing. The phenyl group appeared to be absorbed more quickly than the triazole group, suggesting cleavage of tetraconazole in the gastrointestinal tract prior to absorption. Tetraconazole was broadly distributed to all organs and tissues tested, with the highest level detected in the liver, followed by kidneys, gonads, brain and bones. Low residual levels were still detected in the liver and gastrointestinal tract (sometimes bones) at 72 hr. There was extensive metabolism to polar compounds and excretion primarily in the urine (51-76%) and less in the feces (9-36%) within 48 hr, with only a small portion (≤ 6%) of unchanged parent compound detected in the faeces. Repeated dosing enhanced the rate of metabolism and urine excretion of the chemical, in particular in female rats. Oxidation, reduction and glutathione conjugation were important metabolic pathways.

Acute Studies

Tetraconazole has low oral (LD_{50} 1248 and 1031 mg/kg bw in males and females respectively), dermal (LD_{50} > 2000 mg/kg bw with no deaths) and inhalation toxicity (LC_{50} > 3660 mg/m^3) in rats. It is neither a skin irritant in rabbits, nor a skin sensitiser in guinea pigs, but it is a slight eye irritant in rabbits.

Domark 40ME Fungicide (tetraconazole 40 g/L) is of low oral and dermal toxicity in rats (both LD_{50} >2000 mg/kg bw) and low inhalation toxicity (rat LC_{50} >3170 mg/m^3). It is not irritant to rabbit skin or eyes. It is not a skin sensitiser in guinea pigs.

Short Term Studies

Rats received 0, 40, 160, 640, 2500 or 10000 ppm of tetraconazole in the diet for 4 weeks. All rats at 10000 ppm showed impaired food intake, body weight loss and deteriorated condition. The rats were sacrificed within 5 days, and irregular areas of hepatocyte necrosis and inflammation were revealed at necropsy. Body weight loss and emaciation at 2500 ppm, and reduced body weight gain at 640 ppm were observed, and food consumption was reduced at 160 ppm (females) and above. Rats at 2500 ppm had lower plasma glucose, and higher levels of blood urea nitrogen (BUN), alkaline phosphatase (AP), potassium and inorganic phosphorus, and some of these changes were also seen at 640 ppm. Increased liver weight and enlarged liver were observed in all treated groups, accompanied by a dose-dependent increase in the incidence and severity of hepatocyte enlargement at 160 ppm and above, and hepatocyte vacuolation at 2500 ppm. Reduced weight and small size of uterus were found in females at 2500 ppm.

Male rats received 0, 2, 5, 15 or 40 ppm of tetraconazole in the diet for 4 weeks. No treatment-induced changes were observed except for increased plasma aspartate aminotransferase (AST) and glutamate dehydrogenase at 40 ppm.

Sub-Chronic Studies

Mice received 0, 5, 25, 125 or 625 ppm of tetraconazole in the diet for 13 weeks. In males at 625 ppm and females at 125 and 625 ppm, decreased BUN was detected, and elevated alanine aminotransferase (ALT) and AST activities were associated with increased liver weights. Mice at 625 ppm exhibited pale and enlarged liver with lobular markings accentuated. Hepatocyte enlargement was a major finding in the majority of mice at 25 ppm and above. Hepatocyte necrosis, degeneration or congestion developed at 125 and 625 ppm, and a higher incidence of hepatocyte vacuolation appeared at 625 ppm. Some males at 625 ppm showed lymphocyte aggregation and foci in the kidneys. The NOEL was 5 ppm (1 mg/kg bw/day).

Rats received 0, 10, 60 or 360 ppm of tetraconazole in the diet for 13 weeks. Slightly lower AP, ALT and AST, and slightly higher cholesterol and calcium levels (males) were observed at 360 ppm, and some of these changes also occurred at 60 ppm. Enlarged or swollen liver was seen at 360 ppm. Increased liver weight was associated with minimal centrilobular hepatocyte enlargement at 60 and 360 ppm, and a higher incidence of liver fat deposition at 360 ppm. Increased kidney weight in females and reduced testes weight in males were also observed at 360 ppm. The NOEL was 10 ppm (0.7 mg/kg bw/day).

Chronic & Carcinogenicity Studies

In a carcinogenicity study, mice received 0, 10, 90, 800 or 1250 ppm of tetraconazole in the diet for 80 weeks. Mortality was significantly increased at 1250 ppm. A higher incidence of swollen hard and dark abdomen was noted at 800 and 1250 ppm, which caused moribund sacrifice of some rats at 1250 ppm. Lower body weight gain was observed in mice at 800 and 1250 ppm. In the liver, increased weight and masses and enlarged and discoloured liver were noted at 90 ppm and above with a dose-related increase in the incidence and degree of generalised hepatocyte enlargement, vacuolation, fat deposition and bile duct hyperplasia at 90 ppm (males) and higher doses. There were also increased basophilic hepatocyte foci, eosinophilic hepatocytes, pericholangitis, granulomatous inflammation and pigmented macrophages in mice at 800 and 1250 ppm. Hepatocyte necrosis was detected in some females of each treated group. Kidney weight was increased at 800 and 1250 ppm, along with increased incidences of subcapsular cortical scarring with atrophic tubules, dilated cortical tubules and papillary necrosis at 1250 ppm. Dorsal compression was seen in the brain of some mice at 1250 ppm, and thickening of compact bones in the cranium, ribs and collar bones, myelofibrosis, pale, thickened, broken, chipped and/or overgrown incisors were observed at

800 and 1250 ppm, indicating abnormal bone metabolism. There were small and flaccid testes with reduced spermatogenesis, absence of spermatozoa in epididymides, and small and flaccid prostate and seminal vesicles with reduced secretion at 800 and 1250 ppm, and interstitial cell hyperplasia and prominent multinucleate spermatids in the testes at 1250 ppm. An absence of corpora lutea in ovaries and thin uterus in females were seen at 800 and 1250 ppm. Findings in other organs included enlarged cervical lymph nodes at 800 and 1250 ppm, prominent alveolar macrophages in the lungs of males at 1250 ppm and females of all treated groups, pneumonitis in females at 800 and 1250 ppm, involution in the thymus of males at 1250 ppm, and amyloidosis in various organs of mainly males at 800 and 1250 ppm. Benign and malignant liver cell tumors were increased at 800 and 1250 ppm, and resulted in the high mortality at 1250 ppm. The NOEL was 10 ppm (1.4 mg/kg bw/day).

Rats received 0, 10, 80, 640 or 1280 ppm (the last dose to males only) of tetraconazole in the diet for 2 years; Mortality and body weight gain were lower at 640 and 1280 ppm. Slight anemia at 640 and 1280 ppm was indicated by reduced hemoglobin, hematocrit and erythrocyte counts. In the liver, increased weights, pale areas and accentuated lobular markings were found at 640 and 1280 ppm. Histologically, hepatocyte enlargement, eosinophilic hepatocytes, cystic degeneration (males) and bile duct hyperplasia appeared at 80 ppm and above, vacuolation and fat deposition occurred at 640 and 1280 ppm, and foci of centrilobular inflammatory cells and hepatocyte necrosis were increased in males at 1280 ppm. In the brain of males at 640 and 1280 ppm, dorso-lateral compression, dilated ventricles, and white thickened cranium and parietal bones were probably secondary to the osseous hypertrophy. Increased numbers of rats had pale, thickened and overgrown incisors at 640 and 1280 ppm. Pituitary weights were reduced, with enlarged or vacuolated cells in the pars anterior in males at 640 and 1280 ppm. At interim sacrifice, female rats showed an absence of corpora lutea in the ovaries and a decrease in the incidence of epithelial mucification in cervix and vagina in all treated groups, and squamous metaplasia in the endometrial glands of the uterus at 80 and 640 ppm. At the end of the study, females showed thickened uterus at 640 ppm and males showed a higher incidence of enlarged cervical lymph nodes at 640 and 1280 ppm, along with cystic sinuses at 1280 ppm. Cystic follicular hyperplasia and follicular epithelial hypertrophy were increased in the thyroid of males at 1280 ppm. Tumor incidences were not increased by treatment. The NOEL was 10 ppm (0.4 mg/kg bw/day).

Dogs received 0, 22.5, 90 or 360 ppm of tetraconazole in the diet for 1 year. Some dogs of each group including control suffered body weight loss which was more pronounced at 360 ppm. In dogs at 360 ppm, prolonged activated partial thromboplastin times, lower albumin and higher globulin and cholesterol levels, and increased AP, ALT, gamma glutamyl transferase and ornithine carbamoyl transferase activities, as well as increased inorganic phosphorus were observed. Urinary protein was higher in dogs of this group. Liver and kidney weights were increased at 360 ppm. Histopathology detected apparent hepatocyte enlargement, eosinophilic inclusions in hepatocytes, centrilobular hepatocyte rarefaction, or centrilobular fat in the liver at 90 and 360 ppm, and cortical tubular hypertrophy and apoptotic bodies in the kidneys at 360 and/or 90 ppm. The NOEL was 22.5 ppm (0.7 mg/kg bw/day).

Reproduction Study

Rats received 0, 10, 70 or 490 ppm of tetraconazole in the diet for two generations. F_0 and F_1 females at 490 ppm had reduced food consumption, and lower body weights during premating and gestation, as did F_1 males of this group. Increased mortality (due to dystocia) and higher liver, kidney and ovary weights were seen in adults of both generations at 490 ppm. Mating performance and pregnancy rate for both F_0 and F_1 generations were not affected. A prolonged gestation period was associated with dystocia, and total litter loss in some F_0 and F_1 females at 70 and 490 ppm. Increased post-implantation loss and/or fetal deaths and consequently reduced litter size at birth, and lower pup weight gain during lactation were

observed in F_1 and F_2 pups at 490 ppm. Offspring at 70 and 490 ppm had a slight retardation of growth and sexual maturation (delayed vaginal opening and balanopreputial cleavage). Increased liver weights were seen in F_1 and F_2 pups at 490 ppm as well as female pups at 70 ppm at weaning. No external and internal abnormalities were found for both F_1 and F_2 pups. The NOEL was 10 ppm (0.4 mg/kg bw/day) for reproduction and postnatal toxicity.

Developmental Studies

Pregnant rats received 0, 5, 22.5 or 100 mg/kg bw/day of tetraconazole by gavage on gestation days 6-15. Post-dosing salivation was noted in dams at 22.5 and 100 mg/kg bw/day. Increased water consumption at 100 mg/kg bw/day, and decreased food consumption and body weight gain at 22.5 and 100 mg/kg bw/day were observed. Liver and kidney weights were increased in dams at 100 mg/kg bw/day. There were no treatment-related effects on embryo/fetal loss, litter size and sex ratio of pups. Variable fetal weights within each group at 22.5 and 100 mg/kg bw/day might be associated with variation in degrees of skeletal ossification. Incidences of hydronephrosis and hydroureter at 100 mg/kg bw/day were increased. The number of fetuses with supernumerary rib(s) was higher, and ossification in skeletons tended to be advanced at 100 mg/kg bw/day. The NOEL was 5 mg/kg bw/day for maternal toxicity, and was 22.5 mg/kg bw/day for fetal development.

Pregnant rabbits received 0, 20, 40 or 80 mg/kg bw/day of tetraconazole in a preliminary study, and 0, 7.5, 15 or 30 mg/kg bw/day in the main study, by gavage on gestation days 6-18. Rabbits at 80 mg/kg bw/day showed minimal to nil food intake, body weight loss and deteriorated condition, and were sacrificed on day 7 of dosing showing increased early fetal loss. At 40 mg/kg bw/day, reduced food intake, body weight loss, lower fecal output and emaciation occurred during the dosing period, and increased liver and kidney weight were observed at necropsy. Abortion, death, post-implantation loss, and reduced fetal weight were seen in this group. Food consumption and body weight gain of dams were lower at 30 mg/kg bw/day. Incidences of malformation, anomalies and skeletal variants were low in all groups. The NOEL was 15 mg/kg bw/day for maternal toxicity, and was 30 mg/kg bw/day for fetal growth/development.

Genotoxicity Studies

Tetraconazole was not mutagenic or genotoxic in an Ames test using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, a mouse lymphoma TK locus assay, a chromosomal aberration assay on CHO-K1 cells, a UDS assay *in vitro* and a micronucleus test *in vivo*.

PUBLIC HEALTH STANDARDS

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredients and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning.

The NDPSC has determined that on the basis of its toxicological profile, tetraconazole is to be in Schedule 6 except when it is in Schedule 5. Tetraconazole is in Schedule 5 when it is in preparations containing 20% or less of tetraconazole. There are provisions for appropriate safety directions on the product label.

NOEL/ADI

The Acceptable Daily Intake is that quantity of an agricultural compound which can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor which reflects the quality

of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for tetraconazole was established at 0.004 mg/kg/day based on the NOEL of 0.4 mg/kg/day in the 2-year rat dietary studies and reproduction studies in rats and using a 100-fold safety factor in recognition of the extensive toxicological database available for tetraconazole.

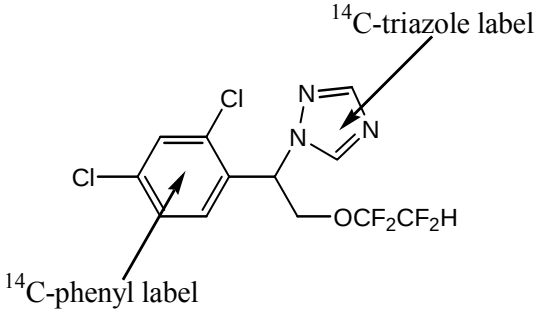
Acute Reference Dose (ARfD)

The acute reference dose is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated, event. The ARfD is derived from the lowest single or short term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

In the 4-week dietary study in rats, the NOEL for clinical signs was 16 mg/kg/day and this is an appropriate endpoint to use in establishing an ARfD. Using a safety factor of 100, the ARfD is 0.2 mg/kg bw.

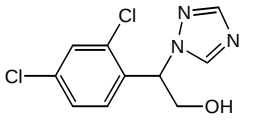
Metabolism

The metabolism of tetraconazole was investigated in plants (grapevines, wheat, sugar beet) and animals (rats and goats) using [phenyl-^{14}C]-tetraconazole and [triazole-^{14}C]-tetraconazole.

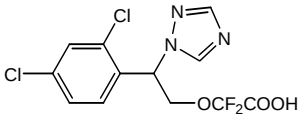


Following application on **grapevines**, appropriately 66-72% of the Total Radioactive Residue (TRR) was extractable from mature grapes. The parent compound contributed 53-55% of the TRR, and no other individual components were present at more than 5% of the TRR. Unextractable residue was associated with cellulose and lignin fractions of the fruit.

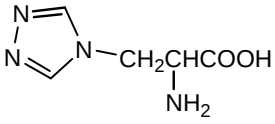
In **wheat** treated with [triazole-^{14}C]-tetraconazole and [phenyl-^{14}C]-tetraconazole, the parent compound accounted for approximately 50% of the straw TRR with smaller amounts of tetraconazole alcohol (0.6% of TRR) and tetraconazole acid (1.6-1.8%). The remainder of the extracted radiolabel was not identified but comprised multiple components including polar metabolites and conjugated species. Approximately 5-6% of the TRR was associated with cellulose and lignin. The TRR was significantly higher in grain that had been treated with the triazole label compared to the phenyl label. In grain harvested from crops treated with the ^{14}C-triazole label only 6% of the TRR was present as parent compound compared to 52% for the ^{14}C-phenyl treatment. Two cleaved metabolites containing the triazole radiolabel, triazolylalanine (50%) and triazolyl acetic acid (25%), were predominant residues in the ^{14}C-triazole treated grain.



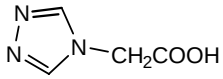
Tetraconazole alcohol



acetic acid

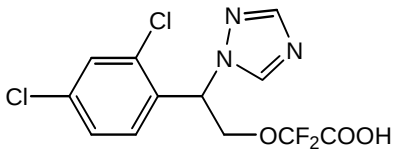


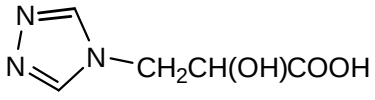
Triazolylalanine



Triazolyl acetic acid

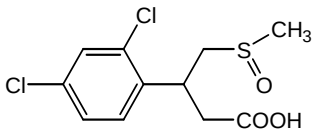
Sugar beet treated with ^{14}C-triazole-tetraconazole had small amounts of radiolabel (ie <0.01 mg equiv./kg) detected in the roots. In leaves, the parent compound accounted for 48% of the TRR (0.7 mg equiv./kg). Identified metabolites included tetraconazole acid (4.8%), tetraconazole alcohol (1.1%) and tetraconazole difluoroacetic acid (9.7%). A number of other metabolites resulting from cleavage of phenyl-triazolyl linkage were also present in leaves, including triazole (5.6%), triazolyl acetic acid (5.6%) and triazolyl propionic acid (7.1%). There was a conversion of tetraconazole to more polar metabolites over time.



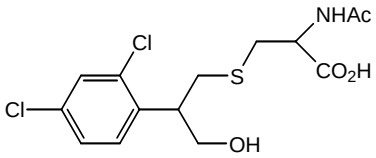


Tetraconazole difluoroacetic acid Triazolyl propionic acid

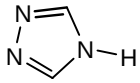
In **rats**, tetraconazole was metabolised to tetraconazole acetic acid and tetraconazole alcohol. The acid and alcohol were converted to metabolites P1 and P4 via glutathione conjugation with production of triazole as a further metabolite. A small amount of parent compound was present in rat faeces.



P1



P4



Triazole

In lactating **goat**s orally fed ^{14}C-triazole labelled test substance at 0.45 mg /kg bw for 5 consecutive days, approximately 4% of the total dose was excreted in the milk, with 41% and 23% recovered in the faeces and urine respectively. Total radioactive residues were highest in liver (3.2 mg equiv./kg) followed by kidney (0.8 mg equiv./kg), fat (0.65-0.84 mg equiv./kg) and muscle 0.33-0.34 mg equiv./kg). The parent compound was the most significant residue in liver (up to 85% of TRR) and fat (up to 80%). Triazole was the most significant residue in milk (up to 78% of TRR), kidney (up to 64%) and muscle (up to 86%). The parent compound was also a significant residue in milk (up to 33% of TRR), kidney (up to 15%) and muscle (up to 12%). The proportion of parent compound residue in kidney increased from 15% of TRR to 46% following incubation with glucuronidase, indicating the presence of significant glucuronide conjugates in the kidney.

In lactating **goats** orally fed 5 consecutive daily doses of ^{14}C-phenyl labelled tetraconazole at 0.45 mg/kg bw, approximately 0.4% of the radiolabel was excreted in the milk with 49% and 27% recovered in the urine and faeces respectively. Total radioactive residues were highest in liver (3.4 mg equiv./kg) followed by kidney (0.87 mg equiv./kg), fat (0.79-0.81 mg equiv./kg) and muscle (0.07 mg equiv./kg). The parent compound was the major residue in liver (86% of TRR), muscle (94%), fat 87-97%) and milk (71-82%). The major radioactive residue in kidney was an unidentified conjugated species (48% of TRR) and the parent compound (32%). The ketone metabolite was a minor component in liver, kidney, muscle and fat (<10% of TRR in all samples). The trifluoroacetic acid metabolite was a minor component in milk (6-15% of TRR).

Residue definition

The available metabolism studies demonstrate that the parent compound is a significant residue in commodities of plant and animal origin. Suitable analytical methods are available to measure residues of tetraconazole parent compound. Therefore, the residue definition will be set as the parent compound only for purposes of dietary assessment and regulatory monitoring.

Tetraconazole tetraconazole

Analytical methods

Samples of grapes and marc/ pomace from the Australian residue trials were analysed using a gas chromatography-mass spectroscopic detector (GC-MS) method that was validated for the determination of tetraconazole. Full details were also provided of an alternative method capable of determining residues of tetraconazole in grapes and animal commodities using gas chromatography- nitrogen-phosphorous detection (GC-NPD) or gas chromatography-electron capture detection (GC-ECD). The method would be suitable for regulatory testing purposes. The limit of quantification (LOQ) for the methods are reported below.

Sample	Technique	LOQ, mg/kg
Grapes	GC-NPD or GC-ECD	0.02
Grapes, marc, dried grapes	GC-MS	0.01
Muscle, fat, liver, milk, kidney, eggs	GC-NPD or GC-ECD	0.01-0.02

Storage stability

Samples from Australian residue trials were stored frozen for a period of ~4-22 months prior to completion of the analysis. In a storage stability study, fortified residues of tetraconazole in grapes were shown to be stable for up to 38 months when samples were stored frozen (-18 °C). Tissue and milk samples from the cow transfer study were stored frozen and extracted within 28 days of collection.

Residue trials

Grapes

A total of eight Australian residue trials were conducted on grapevines. The proposed withholding period of 14 days was addressed in 7 of the trials. Residues of tetraconazole in grapes harvested at 14-15 days after the last of 3 applications at 1-1.7× the proposed rate were, in ranked order: 0.03, 0.03, 0.04, 0.08, 0.11, 0.22 and 0.30 mg/kg. When corrected to a proposed rate of 1.2 g ai/100L, the highest residue (HR) for grapes is 0.18 mg/kg. The corrected STMR is 0.05 mg/kg. An MRL of 0.5 mg/kg is appropriate for grapes with a withholding period of 14 days.

Processing studies

Dried grapes

Dried grapes were produced from treated grapes at two of the trial sites. Residues in dried grapes produced from grapes harvested 14 days after the last application of tetraconazole were 0.13 and 0.40 mg/kg. The respective concentration factors were 0.6 and 1.3. The limited data suggest that tetraconazole residues may concentrate in dried grapes to a limited extent. The corrected HR for fresh grapes is 0.18 mg/kg. Based on a concentration factor of 1.3×, it is concluded that the proposed MRL for grapes (0.5 mg/kg) is likely to be adequate to cover residues in dried grapes.

Wine

Two wine processing studies were conducted in France. Field grown grapevines were treated with 5 applications of tetraconazole at 40 g ai/ha. Grapes were harvested 30-38 days after the last application and processed to red or white wine. Residues of tetraconazole in the raw grapes were 0.04-0.05 mg/kg. Residues in must and wine produced from the treated grapes were all <0.01 mg/kg. Tetraconazole residues are unlikely to concentrate in wine and therefore a separate wine MRL is not required.

Pomace/ marc

Residues in grape marc (also referred to as grape pomace) were determined in three of the Australian residue trials and also the French wine processing studies. The mean concentration factor for all marc samples was 3.5. The dry matter contents of marc samples were not specified, so they are assumed to be 40%. Based on the corrected HR and STMRs for fresh grapes, the HR for grape marc is ~1.6 mg/kg DM and the STMR is 0.46 mg/kg DM. The data support an MRL of 2 mg/kg (dry weight basis) for grape pomace.

Animal commodity MRLs

Processing waste from grapes (ie marc/ pomace) may be used as animal feeds. They are considered fruit by-products, which can be fed to cattle, sheep and pigs up to 20% of dietary intake, and 5% for poultry. In addition, vineyards may be grazed following Domark 40ME Fungicide treatment.

The estimated maximum exposure of livestock to tetraconazole residues is calculated to be ~0.1 ppm in the feed. In the data submission, animal transfer studies were provided for

lactating cows, dosed continuously for 28 days at feed intakes of 0.09 and 0.35 ppm. Residues of fenbuconazole were determined in tissues, milk and eggs. At the expected feeding level of ~0.1 ppm in the diet, it is estimated that fenbuconazole residues in meat and milk will be below the limit of quantification of 0.01 mg/kg for each of these commodities. Liver is the only mammalian commodity expected to contain a detectable residue of tetraconazole following feeding of grape pomace. From these data, the following animal commodity MRLs are recommended:

MO 0105	Edible offal (Mammalian)	0.2 mg/kg
MM 0095	Meat (mammalian) [in the fat]	*0.01 mg/kg
ML 0106	Milks	*0.01 mg/kg

No information was provided on the potential exposure of livestock grazing in treated vineyards. However, metabolism data conducted on wheat show that after treatment at 125 g ai/ha, residues in the foliage at 0 days after treatment were a maximum of 3.55 mg/kg equivalents. When corrected to the proposed rate for grapevines of 12 g ai/ha (ie 1.2 g ai/100L with average spray volume of 1000 L/ha), the anticipated residue level is ~0.34 mg/kg equivalents. Note that this residue level is conservative as it does not relate to the parent compound only, and that residues are likely to decline following treatment. In order to ensure residues are appropriate to the animal commodity MRLs, a 28 day grazing withholding period is proposed for the grazing of treated vineyards. Therefore, the following grazing withholding period is recommended:

Grazing withholding period:

Do not allow livestock to graze treated vineyards for 28 days after application.

Estimated dietary intake

The chronic and acute dietary intake risk for tetraconazole has been assessed. The ADI for tetraconazole is 0.004 mg/kg bw/day, based upon a NOEL of 0.4 mg/kg bw/day and a 100 fold safety factor. The NEDI of flumioxazin is equivalent to 3% of the ADI. With respect to acute dietary intake, an acute reference dose (ARfD) of 0.2 mg/kg bw/day has been set for tetraconazole. The highest acute dietary intake was estimated at less than 2%. It is concluded that chronic and acute dietary exposure to tetraconazole is low and the risk from residues in food is acceptable.

Bioaccumulation potential

The log P value (Log $P_{0/W}$) for tetraconazole is 3.56, indicating that it is likely to have intermediate fat solubility. In lactating cows, tetraconazole showed some concentration in fat compared to muscle tissue. However, bioaccumulation is only short term, as the feeding studies show following a depuration period of 14 days, residues in fat depots declined to <LOQ.

Recommendations

The following amendments to the *MRL Standard* are recommended in relation to the proposed use of Domark 40ME Fungicide:

Table 1

Compound	Food		MRL (mg/kg)
Add:			
Tetraconazole	FB 0269	Grapes	0.5
	MO 0105	Edible offal (Mammalian)	0.2
	MM 0095	Meat (mammalian) [in the fat]	*0.01
	ML 0106	Milks	*0.01

Table 3

Add:	
Tetraconazole	Tetraconazole

Table 4

Compound	**Animal Feed Commodity**		**MRL (mg/kg)**
Add:			
Tetraconazole	AB 0269	Grape pomace, dry	2

The following withholding periods are required in conjunction with the above MRLs:
Grapevines: Do not harvest for 14 days after application.
Do not allow livestock to graze treated vineyards for 28 days after application.

ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD
OVERSEAS REGISTRATION STATUS

Overseas Registration Status

Tetraconazole has not been considered by Codex. The applicant indicated that tetraconazole products are registered for use on grapes in Portugal, Slovak Republic, Spain, UK, Greece, Hungary, Italy, France, Jordan, Taiwan, Iraq, Israel and Brazil.

Overseas MRLs

The following overseas tolerances are indicated to have been established for tetraconazole:

Country	Commodity	Tolerance, mg/kg
France	Grapes	0.2
	Wine	0.02
Greece	Grapes	0.2
Italy	Grapes	0.5
Portugal	Grapes	0.2
Spain	Grapes	0.2
Japan	Grapes	0.5
Taiwan	Small berries	0.5

Potential risk to Australian export trade

Wine

Wine is considered a major commodity export for Australia[1]. The total exports of Australian wine in 2001-2002 were 417 ML valued at $2 billion[2]. The 10 largest export markets for Australian wine by value are shown below[2]:

Destination	Value, $ million
United Kingdom	843
United States	583
Canada	124
New Zealand	85
Germany	48
Ireland	43
Netherlands	33
Japan	30
Switzerland	30
Sweden	25

Overseas processing studies indicate that residues of tetraconazole are reduced in wine compared to fresh grapes. Residues were <0.01 mg/kg in wine produced from grapes containing 0.04-0.05 mg/kg of tetraconazole. The residues in the grapes used for the processing studies were lower than the highest residue observed in grapes from the Australian residue trials. While residues are clearly depleted in wine, it is not certain that they will be <LOQ under Australian production conditions following a 14 day withholding period for grapevines.

[1] Part 5B of the Vet Requirements Series and Ag Requirements Series, Overseas Trade Aspects of Residues in Food Commodities, August 2004.

[2] Australian Commodity Statistics 2002

With respect to wine intended for export markets, the following withholding period is on the label:

> Grapes (Table, Dried, or Wine intended for export): Consult your winemaker, industry spray diary or peak industry body for the recommended withholding period.

The following additional label statement is recommended:

> *Crops producing fruit for export or wine production:*
> *Growers should note that Maximum Residue Limits (MRLs) or import tolerances have not been established in all export markets. Additionally, some export markets have established MRLs different to those in Australia. If you are growing fruit for export (either fresh, dried or for wine production), please check with Sipcam Pacific Australia, your Industry Association or Winemaker BEFORE using Domark 40ME Fungicide.*

The Australian wine industry has mechanisms in place to advise growers on the use of pesticides in wine grapes and manage potential residues in wine through the Australian Wine Research Institute (AWRI). Comment is required from industry on the potential for undue prejudice to exports of wine. The applicant should also consult with AWRI to facilitate an appropriate entry in the Agrochemicals booklet to cover the use of Domark Fungicide on wine grapes.

Table grapes

Table grapes are considered a major commodity export for Australia[3]. Total exports of table grapes in 1999/2000 were 35,129 tonnes valued at approximately $74 million[4]. The 5 largest export markets for Australian table grapes in 1999/2000 are shown below:

Destination	Volume, tonnes	Value, $ million
Hong Kong	11,279	24,809
Singapore	9,718	16,958
Malaysia	4,306	9,352
New Zealand	1,941	4,544
Indonesia	1,531	3,371

Detectable residues are likely to occur in table grapes. There are no import tolerances for tetraconazole residues in/on table grapes in the major export markets (ie Hong Kong, Singapore and Malaysia). In contrast to the wine industry, the table grape industry does not have the same QA programs in place to manage chemical residues in exported produce. The table grape industry should be made aware that residues of tetraconazole may present a risk to Australia's export trade in this commodity. Therefore, comment is sought from the industry as to the impact from the use of Domark 40ME Fungicide on table grapes destined for export.

[3] Part 5B of the Vet Requirements Series and Ag Requirements Series, Overseas Trade Aspects of Residues in Food Commodities, August 2004.

[4] The Australian Horticultural Statistics Handbook

Dried grapes

Dried grapes are considered a major commodity export for Australia[5]. Total exports of dried vine fruits in 1999/2000 were 4,592 tonnes valued at approximately $12 million[6]. The 5 largest export markets for Australian dried vine fruits in 1999/2000 are shown below:

Destination	Volume, tonnes	Value, $ million
Germany	1,471	3,821
United Kingdom	888	2,698
New Zealand	888	2,441
Canada	680	1,827
Belgium-Luxembourg	227	621

Detectable residues are likely to occur in dried grapes. There are no import tolerances for tetraconazole residues in/on dried grapes in the major export markets. The dried grape industry should be made aware that residues of tetraconazole may present a risk to Australia's export trade in this commodity. Therefore, comment is sought from the industry as to the impact from the use of Domark 40ME Fungicide on produce destined for dried grape export.

Animal commodities

Cattle meat and dairy products are major export commodities[5]. The US has established the following time limited tolerances (expiry date 31/12/2005):

Commodity	Tolerance, mg/kg
Cattle, fat	0.6
Cattle, kidney	0.2
Cattle, liver	6.0
Cattle, meat	0.03
Cattle, meat by-products, except kidney and liver	0.03
Milk	0.05

Residues in mammalian meat and milk are expected to be below detectable levels, and thus will not impact upon the trade of these commodities. Liver is the only mammalian commodity to contain detectable residues of tetraconazole, expected to be below the MRL of 0.2 mg/kg. As mammalian liver is not a major commodity for export, it is not likely to prejudice Australian mammalian meat trade.

The risk of detectable residues of tetraconazole in poultry commodities is small as poultry exposure will be negligible (ie <5%). Because of this, MRLs for poultry commodities will not be set at this time.

[5] Part 5B of the Vet Requirements Series and Ag Requirements Series, Overseas Trade Aspects of Residues in Food Commodities, August 2004.

[6] The Australian Horticultural Statistics Handbook

Tetraconazole is not on the NOHSC *List of Designated Hazardous Substances*. Based on the available data, Domark 40ME Fungicide could not be classified as hazardous according to NOHSC *Approved Criteria for Classifying Hazardous Substances.*

Domark 40ME Fungicide has low acute oral, dermal and inhalation toxicity in rats. The product is not a skin or eye irritant in rabbits, and is not a skin sensitiser in guinea pigs. The main hazards associated with repeat exposure to the product are systemic effects on the liver and changes in haematology parameters.

Domark 40ME Fungicide will be formulated and packaged overseas.

The product will be packed in 1 and 5 L plastic bottles made of high-density polyethylene (HDPE).

Use and exposure

Domark 40ME Fungicide is a micro-emulsion formulation, and will be used for the control of powdery mildew on grape vines.

The product will be mixed with water and applied by ground application. The recommended application rate is 30 mL/100 L for dilute spraying and 90 mL/100 L for concentrate spraying in a minimum spray volume of 250 L/ha of water. Maximum of three sprays are recommended per crop season.

End-users may be exposed to the product when opening containers, preparing spray, applying spray, maintaining equipment and clearing up spills. In addition, workers re-entering treated crops to carry out crop management practices can be exposed to product residues.

Exposure during mixing and loading will be largely through dermal contact with the product and the mix solution. The main routes of exposure during application are likely to be dermal and inhalation.

There were no worker exposure studies available for assessment. In the absence of worker exposure data, NOHSC used the Predictive Operator exposure Model (POEM) and the Pesticide Handlers Exposure Database (PHED) to estimate worker exposure to tetraconazole during mixing/loading and application.

The POEM data indicated unacceptable risk (MOE<100) to mixer/loaders when gloves were not worn. MOE became acceptable when workers wore gloves. Risk to applicators was acceptable even without gloves. The PHED data indicated low risk to workers while mixing/loading and application. Both exposure models assume that workers wear at least one layer of clothing (cotton overalls) when performing these tasks.

The risk assessment indicates that cotton overalls buttoned to the neck and wrist, a washable hat and elbow-length PVC gloves should be worn when opening the container and preparing spray. The risk assessment indicates that cotton overalls, a washable hat should be worn when applying the prepared spray by ground application method.

Re-entry

There were no worker exposure data available to assess exposure during re-entry activities. Workers entering treated areas can be exposed to product residues and degradation products during crop irrigation, manual harvesting or other crop management activities. The NOHSC

recommends that re-entry to treated areas is restricted until the spray has dried. If entry is required before this has occurred, workers should wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), impervious gloves, and a washable hat.

Recommendations for safe use

Users should follow the instructions and Safety Directions on the product label. Safety Directions include the use of cotton overalls buttoned to the neck and wrist, a washable hat and elbow-length PVC gloves when opening the container and preparing spray. Safety Directions include the use of cotton overalls buttoned to the neck and wrist and a washable hat when applying the prepared spray.

The PPE recommended should meet the relevant *Standards Australia*.

NOHSC recommends the following re-entry statement on the product label:

RE-ENTRY

"Do not allow entry into treated areas until spray has dried, unless wearing cotton overalls buttoned to the neck and wrist (or equivalent clothing), washable hat and suitable impervious gloves."

Conclusion

NOHSC supports the registration of Domark 40ME Fungicide, containing 40 g/L of tetraconazole, as a micro-emulsion formulation, for the control of powdery mildew on grape vines.

Domark 40ME Fungicide can be safely used by workers when handled in accordance with the instructions on the product label and any other control measures described above.

Additional information is available in the Domark 40ME Fungicide MSDS.

Sipcam Pacific Australia Pty Ltd has applied for the registration of a new product *Domark 40 ME Fungicide* containing the new active constituent (ac) tetraconazole under Category 1 application. The chemical is claimed for the systemic control of powdery mildew on grapevines and is a Group C Fungicide belonging to the DMI group of fungicides. The product will be marketed as a micro-emulsion (ME) formulation with tetraconazole present at a concentration of 40 g/L. The proposed maximum application rate is 18 g ac/ha via ground spraying with no more than two applications per season.

ENVIRONMENTAL FATE

Hydrolysis

Tetraconazole was hydrolytically stable under test conditions at 50^{o}C over the environmental pH range (4-9). Less than 1% degradation was observed at all pHs tested over a period of 5 days at the elevated temperature.

Photolysis

Aqueous: Testing with tetraconazole radiolabelled in the triazole ring in a buffer with pH 7 demonstrated that photodegradation from aqueous solutions is unlikely to occur in the environment. The half life under constant irradiation was around 8 days with the corresponding July and September half lives (Italian conditions) of 68 and 138 days respectively. Several photodegradates were identified. Four photodegradates were found to exceed 10% of the parent dose – FM-2, FM-3, FM-4 and MF-5. The proposed degradation pathway involves ring-cycled formation of the non-polar FM-1 and cleavage of the fluorinated moiety to form the polar FM-8. FM-1 is hypothesised to further degrade to the polar FM-5 which then forms FM-4 and FM-7. FM-8 is predicted to ultimately degrade to FM-7. No soil photolysis studies were provided.

Degradation in Soil and Water

Soils aerobic: ^{14}C-tetraconazole in 4 different soil types were studied. Volatiles were not collected, but the mass balance in each study indicates negligible formation of CO2 or other volatile products. Studies tested the soil system with a non standard protocol in glass containers placed under direct sunlight, and measured daytime temperatures up to 50oC in one study and 46oC in another. These types of temperatures represent a normal temperature at soil surface in field in a summer cloudless day. Degradation did not follow first order kinetics with initial decline being faster than later sampling points. Metabolite formation was essentially the same with SLM-2, SLM-3, SLM-4, SLM-5 and SLM-6 being the main metabolites found. In two soils, SLM-2 and SLM-6 exceeded 10% AR but otherwise, none of the metabolites exceeded this value, and were generally found <5%. The rate of degradation of the parent compound varied between the soils and half-lives ranged from 43 to 191 days indicating the potential for tetraconazole to persist in soils.

Water aerobic: One aerobic experiment was submitted with tetraconazole labelled in the triazole ring. The test system consisted of two separate water/sediment systems, one from a pond and the other from a runoff area. The parent compound disappeared quickly from water bodies (half-life around 2 days for both systems). This corresponded to a rapid increase in chemical found in the sediments where decline was very slow. For the most part, sediments were anaerobic, and the majority of the radioactivity found was parent compound indicating very little metabolism of tetraconazole under anaerobic conditions. For the whole

water/sediment systems, half-lives were calculated as 382 and 318 days for the pond and run-off system respectively demonstrating the persistence of tetraconazole in such systems.

No anaerobic soil or water studies were presented.

Mobility

Volatility: The measured Henry's Law Constant (4.24 X 10-9 atm.m3/mole) suggests very slight volatility from water. Modelling indicates that where tetraconazole is present in the atmosphere, it is unlikely to persist with calculations indicating it would degrade rapidly by reaction with hydroxyl radicals (DT50 around 11.7 hours).
Adsorption/desorption: One batch equilibrium study in 4 soils was provided for tetraconazole radiolabelled in the triazole ring. The chemical showed Koc values ranging from 531 (clay) to 1922 (clay loam), demonstrating low mobility.
Leachability: Column leaching studies were provided with tetraconazole labelled in both the triazole and phenyl rings. A total of 4 different soils were considered. Results were a little variable with some movement down to the 10-15 cm layer found in two soils, and radioactivity (<1% AR) found in the 15-20 cm soil layer. However, very little radioactivity was found in leachates (always <0.15%) and the results tended to demonstrate that tetraconazole is unlikely to undergo significant leaching.

Field Dissipation

Soils: Three field dissipation studies were provided. The first considered accumulation of tetraconazole following several years of application with 2-4 applications per annum. The results of this non-standard study where single sampling each year several months after the final application indicated that there is persistence observed in all sites. However, no accumulation of residues in soils could be observed after residues had been mixed into the 0-30 or 0-60 cm soil profile. Given its importance in addressing accumulation over time from multiple applications, it is recommended that further work be performed in this area with any extension proposal, particularly at higher application rates.

The other two field studies determined tetraconazole residues in soil samples obtained from field tests where tetraconazole was applied as a single dose. The tests were conducted over 1 year to 67 weeks and covered 5 soil types. Both these studies indicated very little movement of tetraconazole with no residues being detected below 10 cm. Degradation rates varied significantly between the soils and half lives ranged from 0.79 weeks (5.5 days) to 69 weeks (483 days). Despite rapid initial degradation in some of the soils, tetraconazole was clearly persistent as over the course of the studies, insufficient degradation occurred to allow a DT90 to be calculated.

Accumulation/Bioaccumulation

The logKow for tetraconazole is 3.56 indicating a propensity to bind to lipids. A bioconcentration study was provided to address potential accumulation in aquatic biota, using rainbow trout as the test organism. The average of the actual BCFs determined were around 25, 56 and 38 for the edible tissues, non-edible tissues and whole fish respectively, indicating the chemical will not be bioconcentrating. The study demonstrated an elimination half-life of 0.2 days or less for edible, non-edible and whole fish portions days following cessation of exposure.

The persistence of tetraconazole suggests potential for soil accumulation, and this appeared to be supported by a separate field study. However, modelling based on application rates proposed for use in Australia indicate the concentration in soil following continual use over

many years will plateau at <0.1 mg/kg soil. Residues studies of the rotation crops over a three years treatment period indicate that residues were not taken up by the rotation crops.

ENVIRONMENTAL TOXICOLOGY

Avian

Tetraconazole may be considered moderately toxic to birds. Bobwhite quail (LD50 = 132 mg/kg) showed themselves to be more sensitive to mallard duck (LD50 >500 mg/kg) in acute oral studies. In two short term dietary studies, mallards (LC50 = 422 ppm) were more sensitive than quails (LC50 = 650 ppm). Only one reproductive toxicity study was performed on the mallard duck. The result of the mallard reproduction study will be used as a surrogate for the bobwhite quail given that exposure was through the diet in the reproductive test. This test returned a NOEC of 10 mg/kg diet for mallard duck.

Aquatic

***Fish*:** Acute toxicity tests were performed on freshwater fish under static renewal or flow through conditions. On the basis of these results, tetraconazole is considered toxic to fish with 96 h LC50s ranging from >2.5-4.3 mg ac/L. Fathead minnow was tested for toxicity to their early life stages. This test established a 34 day NOEC of 1.09 ppm and a LOEC of 3.21 ppm. An acute toxicity study was performed on each of the metabolites SLM-2 and SLM-6 on rainbow trout. The results indicate that metabolite SLM-6 is practically non-toxic to fish whereas metabolite SLM-2 has a 96 h LC50 of 24 mg/L.

Aquatic invertebrates: Tetraconazole and formulated product were tested acutely on one freshwater invertebrate (*Daphnia*) under static conditions and one salt water species of mysid shrimp under static conditions. The 48 h EC/LC50 values derived for daphnia and mysid shrimp were 1.8-3.0 and 0.42 mg ac/L, respectively, indicating tetraconazole is toxic to very toxic to aquatic invertebrates. *Daphnia* were further tested chronically under static renewal conditions. The 21-d EC50 (reproduction) was estimated to be 0.73 mg/L. The NOEC (21-d) was determined to be 0.56 ppm. An acute toxicity study of each of the metabolites SLM-2 and SLM-6 indicates that SLM-6 is practically non-toxic to *Daphnia* while SLM-2 has an acute toxicity of 48 h LC50 of 68 mg/L. A 28 day chronic toxicity study was carried out on the larvae of the sediment dwelling organisms midge *Chironomous riparius*. A 28 day LC50 of 5.3 mg/L for the emergence and development rates indicates that tetraconazole is toxic to *Chironomous riparius.*

Algae and aquatic plants: An acute toxicity study on both the technical tetraconazole and the formulated product was performed on single cell green alga. The results indicate that the technical tetraconazole has a 72 h EbC50 of 0.27 mg/L and an NOEC of 0.14 mg/L. The aquatic plant test (Lemna gibba) showed this species to be very sensitive to the chemical with an EC50 of 0.52-1.56 mg/L and a 7 day NOEC as low as 0.032 mg/L. An acute toxicity study on each of the metabolites SLM-2 and SLM-6 was performed on green alga. The results indicate that SLM-6 is less toxic than SLM-2 which has a 72 h EbC50 of 4 mg/L and a NOECb of ≤1 mg/L, both of which are considered to be toxic.

Terrestrial Toxicity:
Honey bees: Two acute toxicity tests by both the oral and contact routes were performed on honey bees. The lower LD50 (96 h) for the oral and contact tests were calculated to be 16.3 and 27.2 µg ac/bee, respectively. A 96 h NOEC for the acute contact test was not determined.

Earthworms: Four toxicity studies on earthworms indicate that tetraconazole was moderately toxic to earthworms with a 14 d LD50 of 71 mg/kg and a corresponding NOEC of 32 mg/kg. Nitrogen transformation and carbon mineralisation in the soil microorganism test appeared unaffected and comparable to the results obtained from control soil when treated with

tetraconazole at a rate of 375 g/ha. A 14 days acute toxicity study on each of the metabolites SLM-2 and SLM-6 indicates that both are slightly toxic to earthworms.

Arthropods: Several laboratory and field tests were conducted on beneficial arthropods with results being mixed. Beetles were shown to be insensitive to the chemical where they resided in the soil and application was to the soil surface, at concentrations up to 250 g/ha. Testing on green lacewing also showed no effects on mortality, fecundity or fertility up to 250 g/ha. Effects on the predatory mite, *T. pyri*, were tested in the laboratory and the field. Laboratory findings showed the chemical to be harmful at the lowest concentration tested of 40 g/ha in terms of both mortality and fecundity with no eggs being laid by surviving mites. In the field, abundance of mites did not seem affected by this same application rate and after 8 weeks at a field rate of up to 312 g ac/ha. However, the tests only counted motile mite forms so no conclusion on fecundity can be drawn from the field tests. Several tests were performed on the parasitic wasp. The tests showed tetraconazole to be slightly harmful at 260 g/ha. A 14 day exposure test on spiders indicated that tetraconazole is harmless at 125 g ac/ha. A 28 days exposure test on each of the metabolites SLM-2 and SLM-6 on Collembola indicates that these metabolites with LD50>500 mg/kg are slightly toxic to Collembola. However, there were some effects on reproduction for the latter with an EC50 of 251 mg/kg dry soil.

Non-target Vegetation: Two toxicity tests were undertaken on 10 plant species to investigate the effects of tetraconazole on the vegetative vigor and seedling emergence of these plants. The results indicate that the EC25 and NOEC were determined to be >112 g ac/ha and 112 g ac/ha, respectively, during the 14 days exposure.

ENVIRONMENTAL RISK

Although tetraconazole is considered moderately toxic to birds and highly toxic to fish, aquatic invertebrates, algae/aquatic plants and sediment dwelling organisms, the environmental risk to these organisms has been estimated and deemed acceptable. Taking into account the worst-case scenario of 10% run-off and spray drift from ground spraying, it is unlikely that tetraconazole will pose an aquatic risk based on the calculated Q values. Toxicity testing on various plants indicates that tetraconazole is unlikely to have an adverse effect on non-target vegetation at the proposed maximum application rate.

Tetraconazole has been shown to be hazardous to bees, when they are exposed through oral or contact means. Based on testing provided, the chemical may prove toxic to some terrestrial invertebrates, for example, predatory mites in the laboratory. Tetraconazole is considered harmless to beneficial athropods including adult predatory mite at the proposed maximum application rate.

CONCLUSION

On the basis of the data, together with the proposed amendment of the label statement, DEH can recommend that the APVMA be satisfied that the proposed use of the chemical will not lead to an unintended effect that is harmful to animals, plants or the environment at the proposed rate following good agricultural practice.

The main concern is with persistence and accumulation in soils and further work in this area is recommended with any future application involving an extension to higher rates and more frequent applications.

Proposed use pattern

In recent years some fungicides have not performed as well as when first released, due to a shift in sensitivity to the fungicides in some vineyards. DOMARK 40ME Fungicide has controlled powdery mildew as well as TOPAS which is generally considered the 'standard' fungicide in the industry. The use of DOMARK 40 ME Fungicide is likely to have an important role in fungicide management strategies in powdery mildew control in the grape industries.

The label claim is for DOMARK 40 ME Fungicide at 30ml/100L to control powdery mildew when used no more than three times per season in a five spray program. In the trials that were analysed sprays were applied on four occasions and in two trials seven times per season. The claim of powdery mildew control with three sprays of DOMARK 40 ME Fungicide in a five spray program is acceptable as four sprays give adequate control of powdery mildew.

Evaluation of efficacy

Seven field trials were conducted to compare the efficacy of Domark 40 ME Fungicide with standard applications of 'TOPAS'. Treatments were randomised and replicated and applied to red and white grape cultivars known to be susceptible to Powdery Mildew and plots consisted of three or more vines per panel.

The trials were conducted in commercial vineyards subjected to normal disease pressure and the presence of unsprayed plots confirmed the presence of powdery mildew at all sites. Because disease development occurred on unsprayed plots in these trials, the treated plots were subjected to higher levels of inoculum than occurs in many vineyards. At each site, forty or more leaves, or bunches were collected and assessed for disease incidence and severity.

Efficacy data was presented where DOMARK 40 ME Fungicide was applied at rates between 20 – 100ml/100L. In five of seven trials DOMARK 40 ME Fungicide was applied at the recommended rate of 30 ml/100L and provided control as good as or in one trial better than similar programs of the standard TOPAS treatment.

Sprays were applied on four occasions and in two trials seven times per season. Although no data were presented to support the claim of powdery mildew control with three sprays of DOMARK 40 ME Fungicide in a five spray program, the claim is acceptable as four spray programs give adequate control of powdery mildew.

Crop Safety

Efficacy studies indicated that there was no phytotoxicity when rates of up to two to three times the recommended rate were applied to three different grape cultivars. The activity of some DMI based fungicides is reduced when tank mixed with copper fungicides. This should be mentioned on the label if it is likely to be a problem; this concern also applies to sulphur and any commonly used chemicals that are compatible with DOMARK 40 ME Fungicide.

Conclusions

Domark 40 ME Fungicide will be a useful addition to the range of fungicides presently used for control of powdery mildew on grapevines. The claim for the application of three sprays of Domark 40 ME Fungicide at 30ml/100L in a five spray program is recommended. The efficacy reviewer also noted that a five spray program that includes three DOMARK 40 ME Fungicide applications and two of another fungicide at the growth stages indicated gives adequate control of powdery mildew in most situations.

POISON

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Domark® 40 ME Fungicide

ACTIVE CONSTITUENT: 40 g/L TETRACONAZOLE

GROUP	C	FUNGICIDE

For systemic control of powdery mildew on grapevines

Contents: 1 Litre

Directions for use:

Crop	Disease	Rate	Critical Comments
Grape-vines	Powdery mildew (*Uncinula necator*)	Dilute spraying 30 mL/100 L Concentrate spraying Refer to the Mixing/ Application section	Apply as part of a five spray programme : 1) when shoots are 10-20 cm long. 2). pre-flowering. 3.) at flowering 4) After friut set 5) before bunch closure. Do not allow spray intervals to exceed 21 days. In some seasons, additional non-schedule sprays may be necessary later in the season. Do not apply more than 3 sprays of Domark in any one season (part of the Avcare anti-resistance strategy). Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. Do not use in equipment that requires rates greater than 150 ml of chemical /100 L of water. Do not apply in volumes less than 250L/ha.

NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION

Withholding Period:

Grapes (Table, Dried , or Wine for domestic consumption) DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION

Grapes (Table, Dried, or Wine intended for export): CONSULT YOUR WINEMAKER, INDUSTRY SPRAY DIARY OR PEAK INDUSTRY BODY FOR THE RECOMMENDED WITHHOLDING PERIOD

General Instructions

Fungicide Resistance Warning

GROUP	C	FUNGICIDE

Domark is a member of the DMI group of fungicides. For fungicide resistance management this product is a Group C fungicide. Some naturally occurring individual fungi resistant to this product and other Group C fungicides may exist through normal genetic variability in any fungal population. The resistant individuals can eventually dominate the fungal population if these fungicides are used repeatedly. These resistant fungi may not be controlled by this product and other Group C fungicides, thus resulting in a reduction in efficacy and possible yield loss. Since the occurrence of resistant fungi is difficult to detect prior to use, Sipcam Pacific Australia Pty Ltd accepts no liability for any losses that result from failure of this product to control resistant fungi.

Mixing/Application

Half fill the spray tank vat with clean water. Then add the required amount of Domark with agitator going and top up the tank to required level with clean water. Agitate thoroughly prior to and during spraying. When mixing products in same tank always add wettable powders first then soluble concentrates then Domark and other emulsifiable concentrates last, adding extra water after each product.

Dilute Spraying

Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the stage of growth of crop being sprayed. Calibrate and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of run-off. Avoid excessive run-off. The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or specialist advice. Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the

point of run-off. The required dilute spray volume, sprayer calibration and operation may all need to be changed, as the crop grows.

Concentrate Spraying

Use a sprayer designed and calibrated for concentrate spraying (that is a sprayer which applies water volumes less than those required to reach the point of run-off) and matched to the stage of crop being sprayed. Calibrate and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen water volume. Determine an appropriate dilute spray volume (See Dilute Spraying above) for the crop canopy. This is needed to calculate the concentrate mixing rate. The mixing rate for concentrate spraying can then be calculated in the following way:

Example only

Dilute spray volume as determined above: For example 1500 L/ha. Your chosen concentrate spray volume: For example 500 L/ha. The concentration factor in this example is: 3 X (ie 1500 L ÷ 500 L = 3). As the dilute label rate is 30 mL/100 L for grapevines, then the concentrate rate becomes 3 x 30, that is 90 mL/100 L of concentrate spray. The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows. Do not use a concentrate rate higher than that specified in the Critical Comments because a higher rate has not been tested by Sipcam Pacific Australia Pty Ltd. For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

Compatibility

In the case of tank mixing with other products always undetake a physical compatibility test prior to tank mixing.

Protection of Wildlife, Fish, Crustaceans and Environment

Highly toxic to algae, aquatic plants and aquatic invertebrates. DO NOT contaminate streams, rivers or waterways with the chemical or used containers.

Storage and Disposal

Store in the closed, original container in a cool, well ventilated area. Do not store for prolonged periods in direct sunlight. Triple or preferably pressure rinse container before disposal. Add rinsings to spray tank. Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

Safety Directions

May irritate eyes. Avoid contact with eyes and skin. Wash hands after use.

First Aid

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126.

Material Safety Data Sheet

For further information, refer to the Material Safety Data Sheet (MSDS) which is available from the supplier or from our web-site, www.sipcam.com.au.

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Date of Manufacture:

IN A TRANSPORT EMERGENCY **DIAL 000** POLICE OR FIRE BRIGADE FOR SPECIALIST ADVICE, CONTACT UNITED TRANSPORT SERVICES EMERGENCY RESPONSE COORDINATOR: **1800 033 111** (24 HOURS)

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GROUP	C	FUNGICIDE

For systemic control of powdery mildew on grapevines

Contents: 5 Litre

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GLOSSARY

[A glossary containing definitions of technical terms should be included to aid readers without specialist knowledge. It should be remembered that a 'Public Release Summary' must be easily comprehended by competent readers of the general public who may or may not have a background in science. Below are some sample glossary entries. Add and delete entries, as necessary, to aid readers in understanding your PRS.]

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product.
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer.
Chronic	Of long duration.
Codex MRL	Internationally published standard maximum residue limit.
Desorption	Removal of an absorbed material from a surface.
Efficacy	Production of the desired effect.
Formulation	A combination of both active and inactive constituents to form the end use product.
Genotoxicity	The ability to damage genetic material
Hydrophobic	Water repelling
Leaching	Removal of a compound by use of a solvent.
Log P_{ow}	Log to base 10 of octonol water partioning co-efficient.
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light.
Photolysis	Breakdown of chemicals due to the action of light.
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body.
Toxicology	The study of the nature and effects of poisons.

References

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Footnote:
Updated versions of these documents are available on the APVMA website http://www.apvma.gov.au.